EXHIBIT 2

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXAMINER: R. ROSENBERGER : ATTY DOCKET: GK-BIO-292C2

APPLICANT(S): E.W. STARK : GROUP ART UNIT: 2505

SERIAL NO.: 08/385,073 : FILED 02/07/95

TITLE: METHOD AND APPARATUS FOR OPTICAL INTERACTANCE AND TRANSMITTANCE MEASUREMENTS

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Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132

SIR:

I, Karl Norris, hereby declare the following:

I

I have received the Bachelor of Science in Engineering degree from Penn State University in 1942.

II

For more than 37 years I served as a research leader in the USDA Agriculture Research Service developing spectroscopic techniques for measuring the quality of agricultural products. I retired in 1988 as Director of the USDA, ARS, Instrumentation Research Laboratory. I , together with my associates, developed most of the techniques that are now being used for non-invasive spectroscopic measurements. Among these techniques were the pioneering use of near-infrared (NIR) diffuse transmittance, diffuse reflectance, and interactance combined with multiple linear regression and later chemometric techniques for the quantitative and qualitative determination of the composition and physical characteristics of scattering materials. These developments were published in more than 100 scientific papers that I authored or co-authored. As a result, I have received numerous awards, including the Alexander von Humboldt Award for developing NIR technology and the USDA Superior Service Award. I have also been elected a member of the National Academy of Engineering.

Since 1988 I have served as a consultant to industry on the design and application of near-infrared spectroscopic instrumentation. I have also been consulting on medical uses of this technology, particularly for measurement of the oxygen saturation of the brain.

III

I am familiar with the prior art devices which perform optical interactance and transmittance measurements. Specifically, I originally developed the techniques for "interactance" measurements including: 1) illuminating one area on the surface of a sample and measuring the diffuse transmitted light from another area of the sample surface; 2) using fiber optics to illuminate and collect diffusely reflected and transmitted light; and 3) using a single concentric detection ring surrounding a central source of illumination. I was co-author of a paper published in 1984 entitled "A new Approach for Estimation of Body Composition: Infrared Interactance", American Journal of Clinical Nutrition, Vol. 40, pp 1123-1130 which first described and named the interactance optical geometry. Since then, I have designed or studied the design of many such devices. I am also familiar with the work of Jobsis, Ferrari, Delpy, Hanley, and Chance in measuring the oxygen saturation of the brain by near-infrared spectroscopy.

The closest prior art devices are the fiber optic probes for use in contact with the surface of the sample which utilize separated illumination and detection areas to measure absorption within the sample. These all use a single source and a single detection means and therefore provide only one measurement. In many cases of interactance devices, a circular central aperture surrounded by a concentric ring aperture was used, one aperture for the source and the other for detection, in order to maximize the measurement volume for a given path length through the sample. In at least one case, a number of equally spaced parallel slit apertures were used, alternating between source and detection functions, in order to increase the measurement volume. There was still only one detection signal generated and all the parallel paths were of equivalent geometry. In other cases, the source and detection areas were placed on opposite sides of the sample to generate a diffuse transmittance measurement.

Diffuse reflectance, transmittance and interactance measurements made with these single measurement devices have significant problems and shortcomings. Surface effects are a major obstacle, particularly for reflectance where most of the detected signal arises at or very near the surface. The transmittance and interactance optical geometries are specifically designed to eliminate collection of the direct surface reflection. However, in each of these cases the illumination must pass through the portion of the sample near the surface. In many cases, particularly for in-vivo medical measurements, the surface portion of the sample is significantly different from the interior from which information is desired. The simple single source-single detection geometry provides no additional information for discrimination of the effects of the region near the surface from those of the deeper interior portion of the sample. Several investigators have proposed laser pulse time-of-flight or phase detection of very high frequency source modulation to isolate an interior measurement volume in the brain.

The depth of penetration and the path length of the measurement provided by interactance devices is related to the spacing between the source and detection areas. The effective path through the sample is the result of a complex combination of absorption and scattering effects occurring within the volume of the sample. In the simple single source-single detection devices, the depth of penetration and effective pathlength cannot be simultaneously optimized. Increased spacing between the source and detection apertures simultaneously increases the depth of penetration and the effective pathlength. Due to both scattering and absorption losses, increased pathlength rapidly reduces the detected energy and the measurement signal-to-noise ratio. Inhomogeneous samples further complicate the picture. For example, an inhomogeneity located near the central aperture is common to all of the paths through the sample. Consquently, it is unduly weighted in the measurement thereby increasing the error. Layered samples, like skin which is made up of many layers of tissue of different characteristics, provide additional problems. For example, the source energy may be preferentially guided by the structure resulting in systematic errors in the measurement. In essence, the measurement is not being made on the desired portion of the sample. A major shortcoming of the prior art measurement technology is the lack of optimization of the measurement volume. Furthermore, the physics of light transmission through absorbing and scattering media ensures that the resulting measured signal is highly nonlinear with respect to concentration and other properties of the sample that are to be determined.

I have also reviewed the optical geometries of the Borsboom, Hirao and Howarth patents which were cited by the examiner as prior art. Borsboom uses a central source fiber and at least one parallel detection fiber. In addition, he also measures the energy which is reflected or backscattered into the illumination fiber optics as a second detection site. However, this energy is predominately returned from the surface of the sample. It exhibits little or no absorption resulting from interaction with the interior volume of the sample. It appears that Borsboom has physically combined a reflectometer to measure backscatter with a classical single ring interactance probe to measure absorption. He does not cite combining the two measurements in any way to provide an improvement over the problems and shortcomings discussed in the paragraphs above. Furthermore, his second path cannot be adjusted to provide sufficient pathlength for obtaining the necessary absorption signal for use to cancel undesired portions of the absorption signal from the longer path. For this purpose, it is essential to have space between the source and detection areas in order to control the depth of penetration and the measurement volume encompassed by the effective optical path through the sample.

In his more detailed description and explanation, Borsboom refers to "Arranged in a ring ... are four juxtaposed optical fibers 7" while his figure 5 shows a full ring of fibers. There is no written discussion of any advantages of either a full or partial ring over a single juxtaposed detection fiber nor indication that such is a preferred embodiment of his device. In short, Borsboom provides no solutions to the problems listed above.

Hirao and Howarth both use a linear arrangement of source and detection apertures to provide two optical paths defined by one aperture common to the two paths and separate apertures at the other ends of the two paths. Hirao addresses the problems of sample

inhomogeneity and the positional deviations of the measurement apparatus which deteriorate the reproducibility of the result. He apparently wishes to measure a small homogeneous region within the larger heterogeneous material. He uses either one detector and a plurality of sources or a single source and a plurality of detectors to make the measurements. Hirao desires to obtain a commonality of path over the majority of the distance from each measurement point to the common detector or source point. His approach is to obtain information from a very small region in the vicinity where the paths are not common by cancelling the signal common to both paths. His figures 2 and 4 indicate that he does not appreciate the depth of penetration and lateral diffusion differences between the two paths Not withstanding this, his examples 1 and 2 show that the distances from source to receiver are almost the same for the two paths and substantially longer (3 to 6 cm) than the difference in these distances (0.3 to 0.5 cm). This 10:1 ratio of spacing maximizes the commonality of path. Hirao also spaces the pair of apertures defining the measurement volume far from the common aperture so as to avoid the surface effects near the common point. His optical geometry is designed for the measurement of small homogeneous regions of the overall sample and it requires measurement of the small absorption difference between two paths, each of which exhibits high absorption because it must be substantially longer than the path difference which defines the small volume of interest. Use of extended apertures, such as rings, would prohibit such a measurement.

Howarth is concerned with two measurements, the bulk reflectance and the consistency, of paper pulp. The bulk reflectance is measured using the visible wavelength range for sample and the near-infrared range for reference. This measurement is made using a single source aperture and a single detection aperture spaced in the direction of flow of the pulp in order to reduce the effects of consistency variation, pitch buildup on windows, and the boundary layer which adversely affect simple reflectance measurements through a single window. In order to reduce pulp noise, Howarth's apertures are made fully diffusing so that there is no optical directionality of the light within the sample caused by the angle at which the sources or detectors are placed relative to the window. Howarth indicates that the source to detector spacing should be sufficient so that most of the optical paths pass through material that is outside the boundary layer however, every path still includes boundary layer material which is included in the measurement. His reduction in undesired effects results from changing from the reflectance optical geometry to a simple prior art interactance configuration. Howarth also shows that the spacing may be varied to minimize the sensitivity of the bulk reflectance measurement to consistency of the pulp.

Howarth discloses that by using a larger spacing than optimum for bulk reflectance measurements, consistency could also be measured using the above optical geometry. The facts that he uses a single wavelength to measure consistency, that brown and bleached stock have equal response, and that the measurement could not be made if an additional scatterer such as clay or titanium dioxide was added to the pulp indicates that scattering is the basis of the consistency measurement . In order to reduce the effects of pitch and dirt on the windows and pulp noise on this consistency measurement, Howarth states that it is preferred to measure the ratio of received radiation in at least two different window locations. The second window is spaced further from the source than the distance which provides minimum consistency sensitivity

therefore use of this ratio measurement for the bulk reflectance measurement would increase the pulp noise and decrease the accuracy and precision. He provides no discussion of other advantages of such an arrangement and nor does he suggest that it might improve the bulk reflectance measurement, which depends on absorption within the sample rather than only scattering. Thus, the use of a second window and measurement channel was primarily directed to the issue of dirt buildup affecting a scattering measurement in a particular environment. In most cases, there are many approaches to solving this problem more economically and effectively than adding a second channel, for example, the use of a protective film over the measurement tip as suggested by Borsboom.

Howarth does not address depth of penetration, layered and inhomogeneous samples, lateral spreading of the light, or optimizing the effective measurement volume for this single source - two detector configuration. The linear arrangement of source and detectors is far from optimum in maximizing the effective measurement volume while controlling the depth of penetration. Thus it is clear that Howarth did not appreciate the problems solved by the invention of US Patent Application 08/385,073.

In overall summary of the prior art, Borsboom does no more than disclose the basic interactance optical geometry described in the application specification as prior art . For the reasons stated above, neither Hirao nor Howarth disclose any teaching which would lead an individual skilled in the art to the invention made by applicant.

IV

Transmittance and interactance spectroscopy provides a powerful technique for non-invasive measurements on a very wide range of possible samples, but we have not had an optimized geometry for measurements on the human body. The major obstacles have been surface effects, non-linearity, uncontrolled optical path, sample inhomogeneity, and signal-to-noise ratio. There is a long felt need for a device that would reduce or overcome the problems of the prior art devices. In order to reduce the effects of sample inhomogeneity, such a device would maximize the measurement volume for a predetermined aperture spacing and avoid preferentially measuring any region of the sample. . It would control the effective depth from which the measurement is made in order to measure the desired stratum of the sample while reducing surface effects. It would define and limit the effective optical paths within the sample and thereby reduce and stabilize the non-linearity. Finally, it would maximize the optical throughput for both the source and detection functions in order to maximize the signal-to-noise ratio of the measurement.

V

I have reviewed measurements presented in a Declaration executed by Dr. Harry Shamoon which were produced by a device described and shown in US Patent Application No. 08/385,073. These measurements show very promising results in predicting glucose content

of the blood of patients using a new spectrometer incorporating this device. The quality of the measurements indicates that the device provides a significant and unexpected improvement over the prior art devices discussed above. Based on my knowledge of the device geometry, I believe that the dual ring geometry and signal processing has controlled the effective measurement depth thereby substantially reducing the effects of the surface and the layered nature of the human body skin. The symmetry of the device has produced concentric measurement volumes that reduce the effects of lateral spreading of the effective paths, including non-linearity. Each of the measurement volumes is as large as possible for the predetermined spacing of the rings and the signal from the region of the central aperture is cancelled. Both factors are effective in reducing the effects of sample inhomogeneity. In addition, directing the light toward the central aperture has increased the energy density at the detection area compared to the prior art devices, thereby enhancing the signal-to-noise ratio of the measurement.

Finally, the signal-to-noise ratio of the measurements is enhanced by using the rings, with their greater area, as the sources rather than the smaller central aperture. The high numerical aperture and large area of source fibers can readily be filled using a tungsten projector lamp with integral reflector thereby maximizing the energy introduced into the sample. This maximizes the energy density scattered into the detection aperture. The detection area and numerical aperture are limited by the requirements of the spectrometer. However, a small detection area allows use of a small detector. Since the detector noise is proportional to the square root of its area, the small detector area is less of a penalty for signal-to-noise ratio than simple throughput considerations might indicate. A system that uses a monochrometer source with limited throughput at the central aperture and detection through the ring apertures using large area detectors would have significantly poorer performance.

For all the reasons stated above, I believe that the device disclosed in US Patent Application 08/385,073 is a significant and unique improvement over the prior art.

I, Karl Norris, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fines or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Karl H. Norris

Signature of Declarant

Nov. 17, 1996

Date